JACC Vol. 3, No. 3
March 1984:681–9

Prognostic Importance of Digitalis After Acute Myocardial Infarction

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Because previous reports have suggested that digitalis administration may lead to increased mortality after hospital discharge for acute myocardial infarction, the independent importance of digitalis therapy in long-term prognosis after acute myocardial infarction was investigated by analyzing 1,599 patients after definite myocardial infarction. After hospital discharge, mortality rate for the entire group at 4 months was 7.7% and after 1 year 14.2%. At discharge, 36.6% of the patients were taking digitalis. Compared with those not taking digitalis, those taking digitalis had more historical risk factors and a higher incidence of important clinical prognostic variables during the hospitalization. Their cardiac mortality rate after 4 months and 1 year (12.5 and 22.4%, respectively) was significantly higher than that of patients not taking digitalis (5.0 and 9.6%, respectively). Mortality was higher for patients taking digitalis whether or not they had congestive heart failure during hospitalization. However, in a multivariate Cox analysis for 1 year outcome, neither digitalis nor any other medication variable displaced the important clinical variables of age, congestive heart failure during the hospitalization, previous myocardial infarction, maximal heart rate during the hospitalization and previous angina. Quinidine and digitalis at discharge were selected sixth and seventh (not significant) by the analysis.

It is concluded that digitalis therapy at discharge after myocardial infarction was not an independent predictor of late mortality in these patients.

The use of digitalis in patients with acute myocardial infarction has been controversial (1–4). It has been reported (5) that digitalis does not increase the sensitivity of the heart to arrhythmias in the majority of patients with acute myocardial infarction. An increase in the size of infarction after digitalis administration was suspected in one study (6), but was not confirmed later in patients with a large infarction and low ejection fraction (7). The long-term benefits of digitalis therapy in patients with chronic congestive heart failure and sinus rhythm have also been controversial (8–10). However, recently a randomized study (11) demonstrated that long-term digoxin therapy is beneficial for patients with heart failure unaccompanied by atrial fibrillation, particularly if a third heart sound is present.

Toxic reactions to long-term digitalis therapy (12) have raised the suspicion of a negative influence of this drug on mortality. An independent adverse prognostic contribution of digitalis to mortality after acute myocardial infarction has been described (13) using retrospective data to show a 30% increase in mortality rate after 4 months in patients taking digitalis who had congestive heart failure and complex ventricular arrhythmias after adjustment for other relevant characteristics. Also, the 1 year mortality rate after acute myocardial infarction was reported in a preliminary retrospective study (14) to be independently increased by digitalis therapy. However, a recent report from the Coronary Artery Surgery Study registry (15) showed that digitalis therapy was not an independent risk factor in patients in whom follow-up was started within 2 months after acute myocardial infarction.

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This study was supported by SCOR Ischemic Heart Disease Research Grant HL 17682 from the National Institutes of Health, Bethesda, Maryland awarded by the National Heart, Lung, and Blood Institute, Bethesda, Maryland and the U. S. Public Health Service, Department of Health Education and Welfare, Washington, D.C.; and International Research Fellowships 1 F05 TW0 3154-01 and 1 F05 TW0 33088-01 from the Fogarty International Center, the U.S. Public Health Service, Department of Health Education and Welfare, Order of the Eastern Star, California Chapter, San Francisco, the Danish Heart Foundation, Swedish Medical Research Council, Sweden. Manuscript received July 7, 1983; revised manuscript received October 12, 1983, accepted October 14, 1983.

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0735-1097/84/$3.00

JACC Vol. 3, No. 3
March 1984:681-9

To determine whether digitalis therapy independently affects mortality after acute myocardial infarction ideally would require an appropriately constructed prospective, randomized clinical trial. Whether such a trial is ever conducted will be importantly influenced by the results of retrospective studies. The purpose of this study was to examine in a sizable, multicenter patient group whether there is evidence that digitalis therapy at discharge in an independent predictor beyond relevant clinical variables for death or survival within the first year after acute myocardial infarction.

Methods

Patients. The study group consisted of 1,599 patients discharged after definite acute myocardial infarction. The diagnosis of acute myocardial infarction was established by at least two of the following criteria: 1) characteristic chest pain, 2) electrocardiographic changes with evolution of Q waves (transmural infarction), and 3) elevation of serum creatine kinase. Nontransmural infarction was diagnosed by typical ST segment and T wave changes accompanied by at least criterion 3. All patients were admitted to the hospital within 24 hours after onset of symptoms, and there were no further eligibility restrictions.

Data concerning these patients were available from a data base maintained by the Specialized Center of Research (SCOR) for Ischemic Heart Disease at University of California, San Diego, Medical Center. The patients were recruited during 1969 to 1982 from the University of California, San Diego, Medical Center, during 1978 to 1982 from the San Diego Veterans Administrations Hospital, during 1978 to 1982 from the United States Naval Regional Medical Center, San Diego, and during 1977 to 1982 from the Vancouver General Hospital, British Columbia, Canada. Patients were entered into the study in a consecutive manner, but not all patients agreed to enter the study and personnel were not always available to enter patients. However, there is no apparent reason to suspect a selection bias. Over half of all eligible patients from these centers were utilized, and examination of coronary care units registers showed the in-hospital mortality for the patients studied and those not studied to be the same.

Data collection. The four hospitals were all part of a cooperative prospective study with rigid data-gathering specifications and common data-gathering forms. Data before 1978 for the University of California, San Diego, Medical Center and Vancouver General Hospital were gathered on a different, more extensive set of forms, but according to the same procedures. Data were gathered by a research nurse, clinical data were checked by a research physician and all data were screened by computer for completeness and consistency before final entry into the data base. The physician collaborator from Vancouver General Hospital (H.H.) had previously been one of the main participants in the initial years of the study at the University of California, San Diego, Medical Center.

Clinical variables. Our methods of data acquisition and definitions of variables have been reported in detail previously (16). Historical characteristics, physical findings and electrocardiographic, radiographic and laboratory variables from the entire hospitalization were assessed.

The data base was examined univariately for variables that were related to mortality and had a higher incidence of occurrence for patients taking digitalis. Seventeen historical and clinical factors were identified. Age, sex, cigarette smoking, family history of ischemic heart disease before 60 years of age, previous hypertension, diabetes, chronic obstructive pulmonary disease, congestive heart failure, typical angina pectoris and previous myocardial infarction were recorded on admission. During the entire hospitalization period, we included the maximal heart rate recorded, minimal systolic blood pressure recorded, pulmonary venous congestion on any chest X-ray film defined as previously described (17), congestive heart failure (at least two of the following: persistent bibasilar [or higher] rales, third heart sound, pulmonary venous congestion on X-ray film), anterior localization of infarction, ventricular arrhythmias (frequent ventricular premature beats [more than six per minute], ventricular tachycardia [more than three consecutive ventricular premature beats] or ventricular fibrillation) and atrial fibrillation.

In a subgroup of 432 patients, 24 hour ambulatory electrocardiographic monitoring was performed before hospital discharge. Complex ventricular arrhythmias were defined as frequent ventricular premature beats (more than 1 per minute or 30 per hour), multiform ventricular premature beats, couplets, early ventricular premature beats (R on T phenomenon) or ventricular tachycardia (more than three consecutive ventricular premature beats). This test was not performed routinely in our study patients before 1978. It has been our policy to obtain a 24 hour Holter monitor whenever possible since that time, but only about half of our patients have been so studied. Lack of a sufficient number of monitors has been the main obstacle. There were no systematic selection criteria for which patients were monitored; rather, monitoring was subject to equipment availability, and the incidence of risk variables in this patient subset was similar to that in the entire group.

Discharge medication variables. Certain variables concerning medications at hospital discharge were selected a priori for analysis. Because digitalis is generally given to patients with congestive heart failure, it was important to assess this potential interaction. It has been reported that quinidine increases the blood level of digitalis (18,19), so this interaction was also explored. In addition, it might be expected that patients being treated with digitalis and diuretic drugs might have low potassium blood levels. Therefore, the medication variables analyzed included: digitalis

at discharge, digitalis alone (with neither quinidine nor diuretic drugs), digitalis and no congestive heart failure during hospitalization, digitalis and congestive heart failure, congestive heart failure and no digitalis, neither digitalis nor congestive heart failure, digitalis and diuretic drugs, digitalis and quinidine, diuretic drugs alone (without digitalis) and quinidine alone (without digitalis).

Follow-up. Among the 1,599 patients, 1,424 were eligible and had been followed up 4 months after infarction and 1,300 after 1 year. The mean follow-up time was 322 days. Follow-up in our prospective data base is 98.7% at 1 year. Before 1978, 1 year follow-up was about 94%. We routinely contact patients by telephone at 3, 6 and 12 months. Thus, patients not yet contacted at 6 months had been contacted at 3 months.

Information on actual medication status was obtained at follow-up. Among patients discharged on digitalis therapy, 78% were still using digitalis at 4 months and 76% at 1 year. Among patients discharged without digitalis, 14% had digitalis therapy initiated within 4 months and 12% were taking digitalis after 1 year. Because the degree of crossover was relatively small, we analyzed the effects of discharge medication status on mortality up to 1 year.

Information on deaths was obtained from the death certificate or hospital charts in most cases. For some patients, telephone interviews with the personal physician and family members were obtained to clarify details. Only deaths due to cardiac causes were included in the analyses.

Statistical analysis. Univariate statistical analyses by chi-square or t tests were utilized to assess differences in characteristics between patients receiving digitalis therapy and those who were not and for studying the influence of medication variables on mortality. To evaluate the independent importance of prognostic variables, we used the stepwise multivariate Cox regression model (20) available in the Biomedical Computer Programs package of statistical programs (21). This analysis can include patients with incomplete follow-up whose time of survival is known, so that all 1,599 patients could be studied. In the stepwise model, the final number of variables is determined by a criterion of significance.

We report on the variables selected, along with their order of selection, regression coefficients and constants (which can be used to calculate a prognostic score and risk) and special chi-square values showing the significance of their contribution to the model.

To determine whether medication variables had independent value beyond clinical variables, we performed two analyses. First, the Cox analysis was used to select variables from among the clinical factors. Then the important clinical factors were retained, and the Cox analysis was further utilized to select additional factors from among the medication variables and the interactions we considered important.

To test the prognostic schemes, resubstitution was carried out on the original patient population. In this procedure, a prognostic score is first calculated for each patient in the population (sum of each selected variable multiplied by its regression coefficient plus a constant). Predicted risk of death is then calculated using a baseline survival function for the entire population provided by the program:

$$\text{Risk of death} = 1 - \text{baseline survival function}^{\exp(\text{score})}.$$

Patients with a predicted risk of death greater than 10% were classified into the high risk group for death. At 4 months, 1,424 patients could be so classified because their status was known at least 4 months after their acute myocardial infarction; at 1 year, 1,300 patients could be classified. Correct prediction was evaluated by calculating correctly classified deaths (sensitivity for prediction of death), correctly classified survivors (specificity for prediction of survival) and total correct prediction (accuracy of prediction). In addition, the proportion of patients in the high risk group was calculated and the predictive value assessed (mortality in high risk group).

Results

Digitalis use and basic characteristics. The characteristics of patients who were or were not taking digitalis at the time of hospital discharge are presented in Table 1. The incidence of digitalis therapy varied among the four hospitals, with the incidence at the San Diego Veterans Administration Hospital and the University of California, San Diego, Medical Center being similar at about 50% and that at the United States Naval Regional Medical Center in San Diego and Vancouver General Hospital at about 30%.

Patients taking digitalis had a higher incidence of historical findings that were predictive of increased risk, namely, a higher age, more smoking, previous infarctions, angina and congestive heart failure. Also, during the hospitalization these patients had a higher incidence of anterior site of infarction, congestive heart failure and pulmonary venous congestion on chest X-ray film. In addition, patients receiving digitalis who had ambulatory electrocardiographic monitoring exhibited a higher incidence of complex ventricular arrhythmias than did patients not receiving digitalis. Diuretic drugs and quinidine were administered more frequently to patients taking digitalis. Overall mortality rate was significantly higher for patients discharged while receiving digitalis therapy (13 versus 5% at 4 months and 22 versus 10% at 1 year). This was true within each hospital with the exception of the United States Regional Medical Center where mortality rate was not significantly higher for patients discharged while receiving digitalis therapy (Table 1).

Univariate analysis. The absence of both congestive heart failure and digitalis at discharge was a very favorable

Table 1. Percent of Basic Characteristics for Patients With and Without Digitalis at Discharge

	Patients With Digitalis (%)	Patients Without Digitalis (%)	Chi-square
Total (n)	585 (37)	1014 (63)	
USVASD	60 (50)	60 (50)	
UCSD	198 (48)	214 (52)	
USNRMC	56 (29)	140 (71)	
VGH	271 (31)	600 (69)	
Age (mean ± SD) (yr)	66 ± 12	59 ± 12	(t = 11.1)
Men	71	77	6.7
Previous history			
Infarction	35	19	49.8
Angina	49	34	36.5
Hypertension	41	34	6.7
Congestive heart failure	25	3	173.0
Diabetes	17	12	9.9
Cigarette smoking	60	73	27.6
Digitalis at admission	30	4	230.0
Diuretic drugs at admission	26	11	57.9
Hospitalization			
Anterior localization	44	34	16.1
Congestive heart failure	75	41	163.5
Pulmonary congestion	62	37	90.3
Heart rate > 80 beats/min	31	61	77.6
Atrial fibrillation	25	6	118.3
Predischarge ambulatory monitoring			
Data available (n = 432)	32	24	14.0
Any VPB	82	67	11.6
Complex VPB	49	31	14.5
Discharge medication			
Diuretic drugs	47	13	230.0
Quinidine	29	9	5.0
Mortality after discharge			
4 months overall	13	5	24.8
USVASD	17	4	5.4
UCSD	12	5	7.3
USNRMC	7	5	0.3
VGH	12	5	11.5
1 year overall	22	10	34.8
UCVASD	35	14	5.4
UCSD	24	9	5.4
USNRMC	10	11	0.2
VGH	20	9	15.2

A chi-square value of greater than 3.84 corresponds to a two-tailed $p < 0.05$. A t statistic greater than 1.96 also has this interpretation. SD = standard deviation; UCSD = University of California, San Diego, Medical Center; USNRMC = United States Naval Regional Medical Center, San Diego; USVASD = United States Veterans Administration Hospital, San Diego; VGH = Vancouver General Hospital; VPB = ventricular premature beats. Figures in parentheses indicate percent.

prognostic variable (Table 2), with a 2.8% mortality rate at 4 months and 6.7% at 1 year compared with 11 and 19%, respectively, for patients taking digitalis or with congestive heart failure, or both (significant difference). The presence of congestive heart failure during hospitalization in patients not receiving digitalis at discharge also implied a significantly higher rate of mortality compared with patients without congestive heart failure (that is, 8.1 versus 2.8% at 4 months). The combination of digitalis and diuretic drugs did not produce a significantly higher mortality rate compared with digitalis alone. The addition of quinidine to digitalis did not increase mortality significantly.

Multivariate analysis. *Four month mortality.* The clinical variables selected by the Cox analysis are presented in Table 3. Age and maximal heart rate during the hospitalization were the most important. When medication variables were added to the analysis (right portion of Table 3) only two additional variables were selected, the combination of

Table 2. Mortality at 4 Months and 1 Year Related to Discharge Medication Variables Using Univariate Analysis

	Total Group (no.)	Deaths at 4 Months		Total Group	Deaths at 1 Year	
		No.	(%)		No.	(%)
Total	1,424	110	(7.7)	1,300	184	(14.2)
No heart failure and no discharge digitalis	534	15	(2.8)*†	487	33	(6.7)*†
No heart failure and discharge digitalis	132	12	(9.1)	118	17	(14.4)*
Heart failure and no discharge digitalis	370	30	(8.1)†	349	47	(13.5)†
Heart failure and discharge digitalis	388	53	(13.7)*	346	87	(25.1)*
Discharge digitalis	520	65	(12.5)*	464	104	(22.4)*
Discharge digitalis alone	196	20	(10.2)	170	30	(17.6)*
Discharge digitalis and diuretic drugs	250	38	(15.2)*	225	57	(25.3)*
Diuretic drugs alone	118	14	(12.9)	111	18	(16.2)
Discharge digitalis and quinidine	151	16	(10.6)	139	37	(26.6)*
Quinidine alone	84	11	(13.1)	78	15	(19.2)

*Indicates significant difference ($p < 0.05$) between patients with the characteristic compared with all others. †Indicates significant differences between groups adjacent and below. Heart failure indicates congestive heart failure during hospitalization.

no digitalis therapy and no congestive heart failure and administration of quinidine alone. The combination variable was selected first (negative correlation) and discharge quinidine alone (without digitalis) was fifth. The six previously selected clinical variables were retained in almost the same order.

The lower section of Table 3 shows the resubstitution results. No difference in correct classification of death or survival could be detected between using clinical variables alone and with medication variables added. Both sets of variables produced a high risk group for death, consisting of about 25% of the patients with approximately a 19% 4 month mortality rate (predictive value).

One year mortality. Two discharge medication variables, quinidine alone (without digitalis) and digitalis, were selected as the last two variables (sixth and seventh, respectively) (Table 4). However, the chi-square value for digitalis was not significant.

Table 3. Selected Variables and Prediction in Cox Analysis for 4 Month Mortality

	Clinical Variables Alone			Medication Variables Added		
Variables	Order Entry	Coefficient	Chi-square	Order Entry	Coefficient	Chi-square
Age	1	0.042	33.8	2	0.040	21.3
Maximal heart rate	2	0.017	25.3	3	0.017	16.1
Pulmonary venous congestion	3	0.636	13.8	6	0.459	5.7
Previous infarction	4	0.443	8.2	4	0.416	7.7
Minimal systolic pressure	5	−0.013	4.1	7	−0.013	3.8
Previous heart failure	6	0.468	3.7	8	0.485	3.6
No failure, no digitalis	—	—	—	1	−0.554	32.6
Quinidine alone	—	—	—	5	0.823	6.6
Constant		−3.198			−2.800	
Baseline survival function		0.948			0.952	
Classification	Total No.	No. Correct	(%)		No. Correct	(%)
Total	1,424	1,005	(70.6)		1,118	(77.0)
Death	110	69	(62.7)		69	(62.7)
Survival	1,314	1,074	(81.7)		1,027	(78.2)
High risk group		378	(26.5)		356	(25.0)
Predictive value			(18.3)			(19.4)

No failure indicates absence of congestive heart failure during hospitalization.

Table 4. Selected Variables and Prediction in Cox Analysis for 1 Year Mortality

Variables	Clinical Variables Alone			Medication Variables Added		
	Order Entry	Coefficient	Chi-square	Order Entry	Coefficient	Chi-square
Age	1	0.035	41.0	1	0.033	41.0
Congestive heart failure	2	0.612	25.0	2	0.556	25.0
Previous infarction	3	0.487	18.5	3	0.447	18.5
Maximal heart rate	4	0.013	13.5	4	0.012	13.5
Previous angina	5	0.423	7.1	5	0.420	7.7
Quinidine alone	—	—	—	6	0.731	4.0
Digitalis	—	—	—	7	0.292	2.8
Constant		−3.984			−3.844	
Baseline survival function		0.900			0.902	
Classification	Total No.	No. Correct	(%)		No. Correct	(%)
Total	1,300	765	(58.8)		894	(58.5)
Death	184	142	(77.2)		143	(77.8)
Survival	1,116	623	(55.8)		617	(55.3)
High risk group		635	(48.8)		642	(50.1)
Predictive value			(22.4)			(22.3)

Again, the classification results were almost identical for clinical variables alone and with medication variables added (lower section of Table 4). Correct classification of death was very high after 1 year (77 to 78%) but correct classification of survivors was lower (55 to 56%), resulting in lower total correct classification compared with the prediction at 4 months. The high risk group included 50% of the patients with a 22% 1 year mortality rate.

Role of ambulatory electrocardiographic monitoring. The subgroup of patients who had Holter monitoring was classified into four categories, those with and without congestive heart failure during the hospitalization and those with and without complex ventricular arrhythmias (Table 5). At 4 months, in each of the four categories there was a tendency for the mortality rate to be higher in patients taking digitalis, but it was significant only for patients with heart failure and without complex ventricular arrhythmias (16.1 versus 2.3%, $p < 0.02$). The mortality rate was only slightly higher for patients taking digitalis in the group with both congestive heart failure and complex ventricular arrhythmias compared with that for patients not taking digitalis (14.8 versus 12.0%, respectively).

The same tendency was present at 1 year for three of the four categories, with a higher mortality rate in patients taking digitalis and with heart failure but without arrhythmias. Again, this difference was significant only in patients with heart failure without arrhythmias. The mortality rate in the group with congestive heart failure and complex ventricular arrhythmias not taking digitalis was 40% compared with 39% for patients with congestive heart failure and complex arrhythmias taking digitalis (Table 5).

Multivariate analysis of subgroup with ambulatory electrocardiographic monitoring. Only two variables, maximal heart rate and previous history of heart failure, entered when clinical variables, including complex arrhythmias on Holter monitoring, were considered alone for mortality at 4 months (Table 6). When medication variables were also allowed to enter, discharge digitalis and quinidine alone (without digitalis) were the first two variables to enter, with maximal heart rate and a history of previous infarction entered next as variables three and four followed by diuretic drugs alone (without digitalis) as variable five. The percent of deaths correctly identified is higher for the analysis that includes medication variables, but the high risk group was also larger yielding a predictive value (17.3%) identical to that from the analysis utilizing clinical variables alone.

For mortality at 1 year, the results of the Cox analyses were the same, regardless of whether medication variables were allowed to enter (Table 7). A history of previous heart failure, age and the combination of complex arrhythmias on Holter monitoring and congestive heart failure were the only variables selected. It is interesting to note that the predictive value (45.1%) is about twice as high for the comparable analysis in the entire study group (22.4%).

Discussion

This study indicates that patients who are being treated with digitalis at hospital discharge have a higher mortality rate than those not receiving digitalis up to 1 year after acute myocardial infarction. On univariate analysis, mortality was increased in patients taking digitalis, regardless of the presence or absence of congestive heart failure during the hospitalization. It was clear that patients taking digitalis had a greater incidence of important prognostic variables than did patients not taking digitalis (Table 1) and, therefore, it was

Table 5. Mortality in Relation to Digitalis at Discharge, Congestive Heart Failure During Hospitalization and Complex Ventricular Arrhythmias From Ambulatory Monitoring

Variables	Congestive Heart Failure: Absent — Complex Arrhythmias Absent	Absent — Complex Arrhythmias Present	Present — Complex Arrhythmias Absent	Present — Complex Arrhythmias Present
	4 Month Mortality			
Digitalis absent				
No.	90	27	43	25
Death	5	0	1	3
(%)	(5.6)	—	(2.3)*	(12.0)
Digitalis present				
No.	24	18	56	54
Death	3	2	9	8
(%)	(12.5)	(11.1)	(16.1)	(14.8)
	1 Year Mortality			
Digitalis absent				
No.	70	23	34	15
Death	8	2	3	6
(%)	(11.4)	(8.7)	(8.8)*	(40.0)
Digitalis present				
No.	21	16	40	41
Death	4	3	11	16
(%)	(19.0)	(18.8)	(27.5)	(39.0)

*Statistical difference for patients with and without digitalis ($p < 0.05$).

important to adjust for these variables by multivariate analysis. The Cox analysis results indicate that mortality in patients taking digitalis can for the most part be explained by other variables such as age, previous myocardial infarction and congestive heart failure, which contain more prognostic information than do the medication variables. The only exception in the multivariate analysis was the 4 month outcome in the subgroup with 24 hour ambulatory electrocardiographic monitoring. Unfortunately, ambulatory monitoring was not available in all of our patients. The selection of patients appeared to be random, however, because the incidence of variables was similar to that in the entire group of patients. Nevertheless, bias is always possible. Also, the number of deaths by 4 months in this subgroup was small

Table 6. Selected Variables and Prediction in Cox Analysis for 4 Month Mortality for Patients With 24 Hour Ambulatory Monitoring

Variables	Clinical Variables Alone: Order Entry	Coefficient	Chi-square	Medication Variables Added: Order Entry	Coefficient	Chi-square
Maximal heart rate	1	0.022	7.3	3	0.017	3.3
Previous heart failure	2	1.064	6.6	—	—	—
Digitalis	—	—	—	1	1.561	9.8
Quinidine alone	—	—	—	2	1.561	6.4
Previous infarction	—	—	—	4	0.640	3.2
Diuretic drugs alone	—	—	—	5	1.205	2.9
Constant		−2.233			−2.711	
Baseline survival function		0.935			0.950	
Classification	Total No.	No. Correct	(%)		No. Correct	(%)
Total	337	257	(76.3)		238	(70.6)
Death	31	13	(41.9)		18	(58.1)
Survival	306	244	(79.7)		220	(71.9)
High risk group		75	(22.2)		104	(30.9)
Predictive value			(17.3)			(17.3)

Table 7. Selected Variables and Prediction in Cox Analysis for 1 Year Mortality for Patients With 24 Hour Ambulatory Monitoring

	Clinical Variables Alone			Medication Variables Added		
Variables	Order Entry	Coefficient	Chi-square	Order Entry	Coefficient	Chi-square
Previous heart failure	1	0.926	14.3	1	0.926	14.3
Holter arrhythmias and failure	2	0.684	7.4	2	0.684	7.4
Age	3	0.012	4.6	3	0.012	4.6
Constant		−1.850			−1.850	
Baseline survival function		0.863			0.863	
Classification	Total No.	No. Correct	(%)		No. Correct	(%)
Total	260	202	(77.7)		260	(77.7)
Death	53	23	(43.4)		23	(43.4)
Survival	207	179	(86.5)		179	(86.5)
High risk group		51	(19.6)		51	(19.6)
Predictive value			(45.1)			(45.1)

(31 deaths) so that the results of this multivariate analysis should be evaluated cautiously.

Variations in digitalis use in this study. In this multicenter study, clinical practice regarding digitalis therapy differed among the participating hospitals (Table 1). The patients seen at the United States Naval Regional Medical Center include many on active duty and as a group they are considerably younger and have less history of cardiac disease. The overall mortality at both 4 and 12 months is less than for the other hospitals and appears independent of digitalis therapy. Even though the incidence of digitalis therapy at discharge was lower for patients at the Vancouver General Hospital, the mortality for patients using and not using digitals was similar to that of patients at the University of California, San Diego, Medical Center. The overall 1 year mortality was highest for patients at the San Diego Veterans Administration Hospital, and this was reflected in patients both with and without digitalis therapy. The multivariate analyses were repeated including the particular hospital itself as a variable, but this was not selected, indicating that more important prognostic information is provided by the clinical variables.

Effect of patient compliance. It is necessary to consider patient compliance in assessing the impact of digitalis therapy. We found that over 75% of the patients discharged while being treated with digitalis continued digitalis therapy up to 1 year after hospitalization and that 12% of patients not taking digitalis at discharge were using this medication at 1 year. However, we did not measure digitalis blood levels at follow-up, nor was it possible to obtain precise medication information at the time of death. The effects of this degree of crossover on our analyses would be difficult to assess. Therefore, we can present only the prognostic importance of being discharged on digitalis therapy.

Effect of quinidine. It has been reported (18,19) that addition of quinidine increases the blood level of digitalis. However, we could not detect a significantly higher mortality rate in patients discharged while taking both digitalis and quinidine compared with those discharged while taking digitalis alone. Furthermore, the combination variable was not selected by the multivariate analysis, whereas quinidine alone (without digitalis) was selected.

Comparison with previous studies. Our results are in contrast to two previous studies (13,14) but in agreement with a recent report (15), although it is difficult to compare the reports because of differences in methods and study patients. Moss et al. (13) used multiple logistic regression in 812 patients, with mortality at 4 months as the end point. Digitalis was especially important for patients with congestive heart failure and complex ventricular arrhythmias on ambulatory electrocardiographic monitoring. In this group of patients, the predicted mortality rate difference due to an independent contribution of digitalis and adjusted for non-digitalis risk variables was 30%. In no other group of patients was digitalis associated with higher mortality. In our subgroup of patients who had ambulatory monitoring, digitalis use appeared to influence mortality in all categories except patients with congestive heart failure and complex ventricular arrhythmias (Table 5). This difference was statistically significant in patients with heart failure and without complex arrhythmias. In the patients with congestive heart failure and complex ventricular arrhythmias, the 1 year mortality rate was 40% in patients not taking digitalis and was not increased further in patients taking digitalis (39%).

Bigger et al. (14) in a preliminary report, used multiple logistic regression analysis in 490 patients followed up for 1 year. After controlling for complicating clinical variables, digitalis therapy was reported to be significantly associated

with cardiac death, mostly in patients with left ventricular failure or ventricular arrhythmias. An independent prognostic contribution of digitalis was suggested.

In both studies just discussed, the ratio of mortality rates for patients receiving digitalis at discharge compared with those not receiving digitalis (odds ratio) was 3.7 for both 4 months (13) and 1 year (14). In our study, the odds ratio was only 2.6 for 4 month mortality rate and 2.2 for 1 year mortality. It is possible, therefore, that because the strength of association in these other studies was higher, multivariate analysis might show some independent contribution of digitalis to mortality, whereas our study did not.

Ryan et al. (15) recently reported results from a Cox analysis of data in 1,592 patients with acute myocardial infarction within 2 months before entry into the Coronary Artery Surgery Study registry. This group of patients, therefore, is different from those of the two previous studies (13,14) and our study because deaths early after discharge are excluded. The odds ratio for the 4 year mortality rate was 3.6. In agreement with our findings, digitalis therapy could not replace clinical variables. These included the presence of edema, left ventricular wall motion score at cardiac catheterization, number of vessels diseased, age and presence of rales. When these variables were taken into account, the survival curves for patients with and without digitalis were identical up to 4.5 years after entry to the study (15). Although angiographic variables were considered in addition to more easily obtainable clinical variables in the study of Ryan et al., we achieved the same conclusions for the 1 year mortality rate using clinical variables alone.

Conclusions. Although patients taking digitalis have a higher mortality rate after acute myocardial infarction, digitalis therapy is not an independent prognostic factor for long-term mortality when associated clinical variables are considered. Although digitalis was selected as a predictor in the 4 month analysis in the subpopulation with Holter electrocardiographic monitoring, the number of patients in this group was relatively small. Prediction of death or survival at 1 year after acute myocardial infarction by multivariate analysis is the same whether or not medication variables, including digitalis, are utilized in the analysis.

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